MEASUREMENT SYSTEM AND METHOD FOR USE IN DETERMINING THE PATIENT'S CONDITION

FIELD OF THE INVENTION

This invention relates to an optical measurement system and method, as well as an optical probe to be utilized in such system, for use in determining the patient's condition, particularly the ear condition.

BACKGROUND OF THE INVENTION

Non-invasive optical measurements on a patient's body have been developed and are disclosed for example in the following patent publications: US 4,882,492; US 5,001,556; US 5,280,788; US 5,379,764; US 5,582,168; US 6,230,044; US 6,319,199; US 6,379,920; and WO 99/66830. The technique suitable for the diagnosis of ear-related diseases, such as otitis media, is disclosed in WO 02/39874 assigned to the assignee of the present application.

Optical measurements on the patient's ear employ an optical probe such as an otoscope, in which the ear canal is illuminated via a suitable light source. The physician can then view the image directly via an eyepiece mounted to the otoscope, or via a video image, as in US 5,919,130 or US 5,363,839. For reasons of sterility or hygiene and convenience, it is usually appropriate to cover the optical probe with a removable sheath or speculum that prevents contamination to or from the probe, and thus enables the same probe to be used with many patients without the need for sterilizing or disinfecting the probe itself between patients. Typically, the sheath is disposable, and thus made from a low-cost material, thus avoiding the need to sterilize or disinfect the sheath itself after use.

In more advanced systems it may be desirable to improve the quality of the light that is captured from the tissue being investigated, for example the ear canal or the vaginal walls, for the purpose of enhancing the sensitivity of subsequent analyses on this light. In WO 00/74556, for example, an optical probe is provided having an accessory device comprising an integral light-focusing element that enhances the light transmitting functions of the probe, and a window may be provided that acts as an objective for the probe's illumination elements. The accessory device may comprise optical elements such as a system of internal mirrors coupled to the window, or a toroidal ring segment in the form of an annular lens, that allow the device to act as a waveguide to direct light onto target tissues. While the light focusing effect achieved by these arrangements indirectly enhances visualization or data collection, it does not provide a simple and effective mechanism to maximize the quality of transmission of the light reflected or refracted by the tissues via the accessory device itself.

SUMMARY OF THE INVENTION

There is a need in the art to facilitate optical measurements on the patient's body, especially for determining the patient's ear condition, by providing novel optical method and system that enable automatic identification of the patient's ear condition, such as the existence of otitis media, serous otitis media (SOM) or acute otitis media (AOM).

SOM is the medical term for accumulation of fluid within the middle ear cavity. When the fluid occurs, there usually is hearing loss, and there may be a feeling of fullness and pain. SOM often follows an upper respiratory infection, and it is much more common in children four years of age and younger. AOM is the medical term for ear infections. AOM is an inflammation of the middle ear, often accompanied by viral upper respiratory infection.

The technique of the present invention provides for detecting the existence of SOM or AOM condition, and for distinguishing between these conditions. Either one or both of the SOM and AOM conditions can be detected as a condition of the

existence of fluid (mainly water) in the region of interest (ROI). As for distinguishing between the SOM and AOM, this can be based on a difference in the fluid density at the SOM and AOM conditions of the ear. The SOM-related fluid is a transparent glue or clear fluid, while the AOM-related fluid is opaque for visible-range light and therefore is relatively highly scattering for the I.R range. Hence, the fluid which accumulates in the middle ear differently scatters the propagating light, thus a different amount of light is detected at the SOM and AOM conditions. Another way to differentiate between SOM and AOM is by detecting a change in the hemoglobin level in the ROI.

The term ***"region of interest"*** or ***"ROI"*** used herein with respect to this specific application of detecting SOM and AOM, refers to a region including a middle ear cavity between the tympanic membrane and the external inner ear wall (termed "promontory"), as well as the tympanic membrane and the promontory.

According to one broad aspect of the present invention, there is provided a measurement system for use in detecting a predetermined condition of a patient's ear indicative of a certain disease, the system comprising:

(a) an optical measuring unit configured and operable for irradiating a region of interest in the patient's ear with incident light including at least two different wavelengths, detecting light responses of the region of interest to said at least two different wavelengths, and generating measured data indicative thereof, said at least two different wavelengths being selected such that the light response of the region of interest to at least one first wavelength is substantially independent of said predetermined condition and the light response to at least one second wavelength is affected by said predetermined condition; and

(b) a control unit configured and operable for controlling operation of the optical measuring unit, and for receiving the measured data and processing it to generate output data indicative of whether or not said predetermined condition exists, the control unit comprising a memory utility for storing predetermined reference data indicative of the light response of the region of

interest while in a healthy condition of the ear; a data processing and analyzing utility preprogrammed for processing and analyzing the measured data by determining a relation between the measured light responses and the corresponding reference data.

The light response substantial independence of the condition to be detected means that the incident light wavelength is either substantially absorbable by the region of interest (or at least a part thereof) or substantially transmittable by the region of interest, irrespective of the absence/presence and/or change in concentration of substance(s) that are indicative of the predetermined condition. The light response detectable dependence on the predetermined condition of the ear means that the incident light wavelength is differently absorbable/transmittable or scattered by the region of interest when certain substance(s) exists or its concentration has changed in the region of interest, as compared to a normal (healthy) condition when there is no such substance or its concentration is normal in the ROI.

It should be understood that the terms ***"substantially absorbable"*** and ***"substantially transmittable"*** may and may not signify full absorption or full transmission of the specific wavelength, but rather are relative terms meaning that the specific wavelength is relatively higher absorbed or transmitted by the ROI as compared to other wavelengths.

The at least two wavelengths thus include the at least one first reference wavelength and the at least one second operating wavelength. The reference wavelength is either substantially absorbable or substantially transmittable by the ROI irrespective of whether a specific substance exists or its concentration has changes in the ROI. The reference wavelength is thus in at least one of the following wavelength ranges: about 700-900nm and about 1420-1480nm. The at least one operating wavelength is differently absorbable/transmittable or scattered by the region of interest when certain substance(s) exists or its concentration has changed in the region of interest. The operating wavelength is in at least one of the following ranges: about 1200-1400nm and 1500-1700nm. This allows for detecting

a serous otitis media (SOM) condition of the patient's ear; and allows detection of AOM condition by detecting a change in scattering of the operating wavelength (increased scattering or lower intensity of the detected light) from that of the SOM condition.

Preferably, the wavelengths also include at least one additional second wavelength in at least one of the following wavelength ranges: about 540-550nm and 570-580nm, the system being therefore operable to detect an acute otitis media (AOM) condition via detection of a change in the hemoglobin level.

The reference data may be indicative of a relation between the light responses of the healthy ear to the at least two different wavelengths. The measured data is in the form of a relation between the light responses of the region of interest in the patient's ear to the at least two different wavelengths.

The reference data may be indicative of the light response for the operating wavelength as a function of the light response for the reference wavelength corresponding to the healthy condition. The control unit is configured and operable to process the measured data to determine the light response for the operating wavelength as a function of the light response for the reference wavelength, $I^{(w)}_{\lambda oper}=f_1(I_{\lambda ref})$, and determine a difference between the reference and measured data indicative of whether fluid media exists in the region of interest being therefore indicative of the SOM condition.

The reference data may be indicative of the light responses for the second operating wavelengths as functions of the light response for the reference wavelength corresponding to the healthy condition. The control unit operates to process the measured data to determine the light response for the second operating wavelength as a function of the light response for the reference wavelength, $I^{(w)}_{\lambda oper}=f_1(I_{\lambda ref})$, and the light response for the additional second operating wavelength as a function of the light response for the reference wavelength, $I^{(w)}_{\lambda oper}=f_2(I_{\lambda ref})$, and determine differences between the reference and measured data indicative of whether fluid media exists in the region of interest and whether there

is a change in the hemoglobin concentration as compared to that of the healthy condition, being thereby indicative of the AOM condition.

According to another broad aspect of the present invention, there is provided a measurement system for use in determining a patient's condition, the system comprising:

(a) an optical measuring unit operable for applying spectral measurements to the region of interest in a patient's body with predetermined light spectrum and producing measured spectral data indicative thereof; and

(b) a control unit for receiving and processing the measured data to generate output data indicative of the measurement results, the control unit comprising a memory utility for storing predetermined reference data representative of a value or a range of values for at least one predetermined measurable parameter corresponding to a healthy condition of a patient; a data processing and analyzing utility preprogrammed for processing and analyzing the measured data by selecting a certain part of the measured data within at least one range of the predetermined light spectrum and applying a predetermined model to the selected part of the measured data to determine a corresponding value of said at least one predetermined measurable parameter for the measured patient and to generate said output data indicative of association between the determined parameter value and the reference data.

Preferably, the processing of the measured spectral data comprises normalizing the measured spectral data to thereby obtain a relative spectrum. The predetermined model is then applied to the relative measured spectrum.

The normalization of the measured spectral data includes normalization by a reference spectrum, and preferably also normalization by a certain wavelength from the predetermined light spectrum. The result of normalizing the measured data by the reference spectrum is a normalized reflectivity spectrum.

The reference spectrum is indicative of the light intensity illuminating the region of interest as a function of wavelengths of said predetermined incident light.

Generally, this can be implemented by operating the measuring unit to apply spectral measurements to a highly reflective (preferably highly diffusedly reflective) surface. Preferably, this is achieved by appropriately configuring the measuring unit, for example, by providing a plug that has a highly diffusedly reflective surface and is mounted on the measuring unit such that it is shiftable from its operative position when said surface is located in the optical path of light propagating through the measuring unit and an inoperative position of the plug when said surface is out of the optical path of said light. Hence, the measuring unit can be operated to selectively obtain the reference spectrum or the measured data.

Generally, the at least one selected range of the predetermined light spectrum is defined by the patient's condition to be detected. For example, for the purposes of determining the existence of otitis media condition in the patient's ear, the predetermined light spectrum is preferably within 300-1100nm. The selected spectrum preferably includes a range of 500-650nm, and/or a range of 800-950nm.

The data processing with the predetermined model preferably includes: applying a Likelihood Algorithm to the relative measured spectrum, calculating a feature vector as a function of wavelength within the selected range, and calculating a log-likelihood ratio between the feature vector of the relative measured spectrum and that of the reference data. This ratio is scalable to determine the at least measurable parameter indicative of the patient's condition. Preferably, the control unit is configured as an expert system capable of periodically analyzing the calculated measurable parameters and optimizing the model accordingly.

Preferably, the processing of the relative measured spectrum allows for determining two measurable parameters indicative of the existence in the patient's ear of, respectively, serous otitis media (SOM) and acute otitis media (AOM).

The normalizing of the measured spectral data by the reference spectrum may be carried out by presenting the measured spectrum $E_j(\lambda,t)$ and the reference spectrum $W_j(\lambda,t)$ as, respectively,

$$E_j(\lambda,t) = A\, I_j(\lambda,t)\, R_E(\lambda)\, D_j(\lambda,t) \text{ and } W_j(\lambda,t) = B\, I_j(\lambda,t)\, R_W(\lambda)\, D_j(\lambda,t)$$

wherein j is the number of the measuring unit, t is the time, λ is the wavelength

of incident light, A and B are unknown amplitudes, $I_j(\lambda,t)$ is the illumination spectrum of light source for the measuring unit j; $D_j(\lambda,t)$ is the light response spectrum of a detector assembly of for measuring unit j; $R_E(\lambda)$ is the reflectivity spectrum of the region of interest; and $R_W(\lambda)$ is the reflectivity of a reference surface used in obtaining said reference spectrum, the normalized reflectivity spectrum being thus determined as:

$$R(\lambda) = E_j(\lambda,t) / W_j(\lambda,t) = C\, R_E(\lambda) / R_W(\lambda),$$

wherein parameter *C* is a light signal amplitude depending *inter alia* upon a signal integration time and a distance between the measuring unit and the region of interest.

The normalized reflectivity spectrum can be further normalized by a certain wavelength λ_0 within the selected spectrum range, such that all the light intensities are measured relative to the intensity at wavelength λ_0. Hence, the effect of parameter *C* can be eliminated. This can be implemented by setting a relative spectrum $r(\lambda) = R(\lambda) / R(\lambda_0)$ so that $r(\lambda_0) = 1$. The selected value of λ_0 is the center of the wavelength range of the predetermined incident light.

Preferably, the creation of the reference data and the model includes sampling a spectrum $r(\lambda)$ at certain discrete wavelengths, to generate a feature vector $\underline{r} = \{ r(\lambda_n), n = 1, 2 \ldots N \}$; learning probability densities $f(\underline{r} \mid A)$ and $f(\underline{r} \mid B)$ for populations including (A) healthy ears and (B) infected ears; and defining the value or range of values as a threshold T1 chosen to achieve a desired level of sensitivity corresponding to the probability of correctly diagnosing the existence of the predetermined condition of the patient's ear. The probability densities may for example include Gaussian probability densities $f(\underline{r} \mid A) = g(\underline{r}, \underline{\mu}_A, P_A)$ and $f(\underline{r} \mid B) = g(\underline{r}, \underline{\mu}_B, P_B)$, wherein $g(\underline{r}, \underline{\mu}, P) = [\, 2\pi \det(P) \,]^{-N/2} \exp [\, -1/2\, (\underline{r} - \underline{\mu})^T P^{-1} (\underline{r} - \underline{\mu}) \,]$, $\underline{\mu} = \text{mean}(\underline{r})$, $P = \text{covariance}(\underline{r}) = \text{NxN matrix}$. The measured feature vector is then processed to determine the log-likelihood ratio as

$$L1(\underline{x}) = 2 \log \{ f(\underline{x} \mid B) / f(\underline{x} \mid A) \}$$

$$= (\underline{x} - \underline{\mu}_A)^T P_A^{-1} (\underline{x} - \underline{\mu}_A) - (\underline{x} - \underline{\mu}_B)^T P_B^{-1} (\underline{x} - \underline{\mu}_B)$$

Then, the association between this ratio and the predetermined threshold value T1 is determined which is indicative of the existence of the otitis media in the patient's ear.

The technique of the present invention provides for identifying whether the otitis media includes serous otitis media (SOM) or acute otitis media (AOM). To this end, the creation of the reference data and the model includes defining the value or range of values as a threshold T2 chosen to achieve a desired level of sensitivity corresponding to the probability of correctly diagnosing the existence of (B1) the serous otitis media (SOM) and (B2) acute otitis media (AOM). The measured feature vector is processed to determine the log-likelihood ratio as:

$$L2(\underline{x}) = 2 \log \{ f(\underline{x} \mid B_2) / f(\underline{x} \mid B_1) \}$$

$$= (\underline{x} - \underline{\mu}_{B1})^T P_{B1}^{-1} (\underline{x} - \underline{\mu}_{B1}) - (\underline{x} - \underline{\mu}_{B2})^T P_{B2}^{-1} (\underline{x} - \underline{\mu}_{B2}),$$

and then the association between the ratio L2 and the predetermined threshold value T2 is determined being indicative of whether the detected otitis media is SOM or AOM.

Additionally, the technique of the present invention allows for conducting qualitative measurements at the same time as allowing the user (physician) to observe the target tissue itself. This is implemented by configuring the measuring unit (an optical probe) for transmitting light emanating from a target tissue (region of interest) along at least two separate optical channels. The probe comprises a probe head and a speculum member removably fitted to a distal end of the probe head. The probe head comprises light transmission means for directing an illuminating light to said target tissue via a distal end of the speculum, and means for directing light emanating from the target tissue along at least two separate optical channels. The speculum member is adapted for positioning the distal end thereof proximate to the target tissue. The distal end of the speculum member comprises an optical aperture for enabling illuminating light and emanating light to pass therethrough from and to the optical probe. The at least two separate optical channels comprise a first channel for enabling qualitative analysis of said light

emanating from said target tissue, and a second channel for enabling quantitative analysis of said light emanating from said target tissue.

Preferably, the speculum member comprises an internal reflecting mirror for directing illuminating light from the light transmission means to said distal end. The probe head comprises a beam splitter arrangement for splitting light traveling in a proximal direction from said distal end into said first channel and said second channel. The term "beam splitter arrangement" refers herein to any optical arrangement capable of splitting a light beam into at least two beams, i.e., two channels or directions, substantially unaffecting the intensity or wavelength of the light. Preferably, the beam splitter arrangement comprises a parabolic mirror having an aperture therein. Alternatively, the aperture may be replaced with a plug of transparent material, which preferably non-diffracting. The aperture is configured for directing a first portion of light traveling from said distal end therethrough along the first channel and towards an objective. The latter may comprise an eyepiece ocular, or a suitable camera means for recording said image. The parabolic mirror may comprise an optical focusing element for directing a second portion of said light traveling from said distal end along said second channel and towards a light sensor.

Alternatively, or additionally, the speculum member may comprise a suitable first waveguide for directing illuminating light from said light transmission means to said distal end. The first waveguide is in the form of a first layer of material having waveguiding properties comprised in said speculum member, and the first layer having a transmitting face proximate to said distal end, and a first mating face in optical communication with said transmitting face and adapted for enabling illumination light from said light transmission means to pass therethrough to said transmitting face when said speculum member is fitted to said probe head. The light transmission means may comprise a second mating face configured to provide optical communication between said light transmission means and said first mating face when said speculum member is fitted to said probe head.

Preferably, the speculum member is disposable after use with one patient.

The speculum member preferably further comprises a plug removably fitted to said distal aperture, said plug configured to diffusedly reflect incident light thereon from said light transmission means in a known manner. The plug attachment to the speculum may be such that after shifting it into an inoperative position to be out of the optical path, it cannot be returned into the operative position, thus requiring replacement of the entire speculum by a new one.

The present invention thus provides an improved optical probe which enables qualitative measurements to be taken in parallel to enabling observation of the tissue. The probe improves the quality of transmission therethrough of the light reflected or refracted by the tissues. The probe is relatively simple in construction and simple to use, and is relatively inexpensive to manufacture.

Thus, according to yet another broad aspect of the present invention, there is provided an optical probe for transmitting light emanating from a target tissue along at least two separate optical channels, comprising a probe head and a speculum member removably fitted to a distal end of said probe head, wherein:

said probe head comprises light transmission means for directing an illuminating light to said target tissue via a distal end of said speculum, and means for directing light emanating from said target tissue along at least two separate optical channels; and wherein

said speculum member is adapted for positioning said distal end thereof proximate to the target tissue.

According to yet another aspect of the invention, there is provided a measurement system for use in determining the patient's condition, the system comprising an optical measuring unit operable for carrying out spectral measurements, the measuring unit comprising a light source system for generating light of predetermined wavelengths, a detector for collecting light impinging thereon and generating data indicative thereof, said measuring unit comprising a plug that is shiftable between its operative and inoperative positions so as to be, respectively, in and out of the optical path of light propagating from the light source system and having a highly diffusedly reflective surface, the measuring unit being

selectively operable to apply spectral measurements to said surface and obtain reference spectrum data indicative of the reflectance of incident light from said surface and to apply spectral measurements to the region of interest on patient's body to obtain measured spectral data indicative of the reflectance of the incident light from the region of interest.

The system comprises or is associated with a control unit for receiving and processing the measured data to generate output data indicative of the measurement results. The control unit comprises a memory utility for storing predetermined reference data representative of a value or a range of values for at least one predetermined measurable parameter corresponding to a healthy condition of a patient and for storing the reference spectrum; a data processing and analyzing utility preprogrammed for processing and analyzing the measured data by

- selecting a certain part of the measured data within at least one range of the predetermined light spectrum and normalizing said selected part of the measured data by the reference spectrum to thereby obtain a relative measured spectrum;
- applying a predetermined model to said relative measured spectrum to determine a corresponding value of said at least one predetermined measurable parameter for the measured patient and generate said output data indicative of association between the determined parameter value and the reference data.

According to yet another aspect of the invention, there is provided a method for processing spectral measured data to enable determination of a patient's condition, the method comprising processing the spectral measured data indicative of reflection of predetermined incident light from a region of interest as a function of wavelengths of the incident light; said processing comprising selecting a predetermined part of the measured spectral data corresponding to at least one range of the predetermined incident light, normalizing the selected measured data to obtain a relative spectrum, and applying a predetermined model to the relative spectrum to determine a corresponding value of at least one predetermined

measurable parameter and to generate output data indicative of association between the determined parameter value and preset reference data, said reference data being representative of a value or a range of values for said at least one predetermined measurable parameter corresponding to a healthy condition of a patient.

According to yet another aspect of the invention, there is provided a method for use in detecting an SOM or AOM condition of a patient's ear, the method comprising illuminating a region of interest in the ear by at least two wavelengths, detecting light responses of the region of interest to said at least two different wavelengths, and generating measured data indicative thereof, said at least two different wavelengths being selected such that the light response of the region of interest to at least one first wavelength is substantially independent of said condition and the light response to at least one second wavelength is affected by said condition.

According to yet another aspect of the invention, there is provided a method for use in detecting an SOM or AOM condition of a patient's ear, the method comprising illuminating a region of interest in the middle ear by at least two wavelengths, detecting light responses of the region of interest to said at least two different wavelengths, and generating measured data indicative thereof, said at least two different wavelengths being selected such that at least one first wavelength satisfies at least one of the following: is substantially absorbable by water or is substantially transmittable by water the light response to said first wavelength being therefore substantially independent of said condition, and the at least one second wavelength being partially absorbable by water the light response to said at least one second wavelength being therefore affected by said condition.

According to yet another aspect of the invention, there is provided a method for use in detecting an SOM or AOM condition of a patient's ear, the method comprising illuminating a region of interest in the middle ear by at least three wavelengths, detecting light responses of the region of interest to said at least three different wavelengths, and generating measured data indicative thereof, said at least three different wavelengths being selected such that at least one first wavelength

satisfies at least one of the following: is substantially absorbable by water and substantially non-absorbable by hemoglobin, and is substantially transmittable by water and substantially non-absorbable by hemoglobin; the light response of the region of interest to said at least one first wavelength being therefore substantially independent of said condition, the at least two second wavelengths including a wavelength that is partially absorbable by water and a wavelength that is relatively highly absorbable by hemoglobin the light response to said at least two second wavelengths being therefore affected by said condition.

According to yet another aspect of the invention, there is provided a method for use in detecting an SOM or AOM condition of a patient's ear, the method comprising illuminating a region of interest in the middle ear by at least two wavelengths, detecting light responses of the region of interest to said at least two different wavelengths, and generating measured data indicative thereof, said at least two different wavelengths being selected such that at least one first wavelength satisfies at least one of the following: is substantially absorbable by water or is substantially transmittable by water, the light response to said first wavelength being therefore substantially independent of said condition, and the at least one second wavelength being partially absorbable by water the light response to said at least one second wavelength being therefore affected by said condition, a change in the intensity of the detected light of said at least one second wavelength from a corresponding intensity for a healthy condition being indicative of the SOM or AOM condition, and a decrease in the intensity of the detected light to said at least one second wavelength from that corresponding to the SOM condition being indicative of the AOM condition.

According to yet another aspect of the invention, there is provided a method for use in determining a patient's condition, the method comprising:

(i) providing reference data representative of a value or a range of values for at least one predetermined measurable parameter corresponding to a healthy condition of a patient, and a certain reference spectrum corresponding to reflectance of a predetermined light spectrum from a reference highly reflective surface;

(ii) applying spectral measurements to a region of interest on the patient's body with predetermined light spectrum and producing measured spectral data indicative thereof; and

(iii) processing the measured data to generate output data indicative of the measurement results, said processing comprising selecting a part of the measured data within at least one range of the predetermined light spectrum and applying a predetermined model to the selected part of the measured data to determine a corresponding value of said at least one predetermined measurable parameter for the measured patient and generate said output data indicative of association between the determined parameter value and the reference data.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, preferred embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1A exemplifies a block diagram of an optical probe according to the invention;

Fig. 1B illustrates the water transmission spectra for the depth of water of 0.3mm and 5mm, theoretically calculated from the water absorption coefficient spectra;

Fig. 1C shows the experimental results of using the technique of the present invention for detecting the SOM condition;

Fig. 1D illustrates the simulation results of using the technique of the present invention for determining the AOM condition;

Figs. 1E and 1F exemplify a fibers' arrangement suitable to be used in the probe of Fig. 1A;

Fig. 2 is an isometric sectional side view of an optical probe according to another example of the invention;

Fig. 3 is a cross-sectional side view of an optical probe according to yet another example of the invention;

Fig. 4 shows in greater detail the distal end of the probe of Fig. 3;

Fig. 5 schematically illustrates an optical measurement system according to the invention for use in determining the condition of a patient's ear;

Figs. 6A and 6B show two examples, respectively, of a method according to the invention;

Figs. 7A and 7B exemplify a calibration step showing, respectively, the ear spectrum (measured spectral data) and white spectrum (reference spectral data);

Figs. 8A and 8B show experimental results of another example of the method of the present invention for determining the otitis media in the patient's ear.

DETAILED DESCRIPTION OF THE INVENTION

The present invention in its one aspect relates to an optical probe for measuring in a patient's ear. **Fig. 1A** is a block diagram of an optical probe **1** configured as an otoscope. The probe **1** includes an illumination unit **4** having one or more light sources – two light sources LS_1 and LS_2 in the present example; a detection unit **6** having one or more light detectors – two light detectors LD_1 and LD_2 in the present example; and a light directing assembly **7** including one or more optical fibers – six fibers in the present example. Also optionally provided in the light directing assembly is a filtering unit **8** accommodated in the optical path of light emerging from the fibers and propagating towards the detectors and configured for separating between light portions of different wavelengths. The filtering unit **8** includes one or more spectral filters (e.g., dichroic beam splitter, grating, resonator filter). In the present example, the filtering unit **8** includes a dichroic mirror **8A**, and also a mirror **8B** the provision of which is optional (the second detector LD_2 may be located in the optical path of light reflected from the dichroic mirror **8A**).

It should be noted that, generally, the illumination unit and/or the detection unit and/or the light directing assembly may be mounted inside the common housing; or the light sources and/or detectors may be mounted outside the housing and be connected to the inside of the housing via the fibers.

In the present example, the probe **1** is configured and operable to monitor SOM and AOM conditions. In order to monitor the SOM or AOM condition, the probe is configured to detect the existence of fluid media within the middle ear region, constituting a region of interest (ROI). In order to distinguish between the SOM and AOM conditions, the probe is configured to detect a change in the hemoglobin concentration level in the Tympanic membrane. In this connection, the term *"middle ear"* refers to a region including either one or both of the tympanic membrane, and the middle ear cavity between the Tympanic membrane and the Promontory.

Generally, according to the invention, in order to monitor such condition(s) of the ROI as the existence and/or a change in concentration (e.g., over-concentration) of a certain substance in the ROI, the illumination unit of the present invention is configured and operable to produce light including a wavelength or wavelength range selected such that a light response of the ROI to this wavelength depends on the predetermined condition of the ROI. Preferably, however, in order to calibrate the device and in order to take into account various tissue-associated effects, the illumination unit is configured to produce light including at least two different wavelengths or wavelength ranges. At least one of these wavelengths, termed *"reference wavelength"*, is selected such that a light response of the ROI to this wavelength (reflection of the ROI) is substantially independent of the predetermined condition (i.e., of whether the specific substance exists in the ROI and/or the concentration of a specific substance in the ROI has changed from a normal value or range of values). This means that the ROI or at least a part thereof either substantially absorbs or substantially transmits the reference wavelength, irrespective of presence/absence or a change in a concentration of the substance of interest in the ROI. At least one other wavelength, termed *"operating wavelength"*, is selected such that the light response of the ROI to this operating wavelength (reflection) depends on the predetermined condition of the ROI. This means that existence of certain substance or a change of the concentration of the substance of interest affects the absorption/reflection of the operating wavelength. It should be

noted that the term *"reflection"* used herein refers to both specular reflection and scattering.

It should be understood that in order to produce such at least two different wavelengths, either a single light source is used producing broadband illumination including the required wavelengths, or separate light sources are used each for generating the required wavelength(s).

In order to monitor such a condition as the existence of fluid media (mainly water) in the middle ear, the reference wavelength $\lambda^{(w)}_{ref}$ and operating wavelength $\lambda^{(w)}_{oper}$ are preferably selected to be, respectively, of about 1420-1480nm or 700-900nm, and of about 1200-1400nm or 1500-1700nm.

The reference wavelength range of 1420-1480nm is highly absorbable by water and is thus highly absorbable by the tympanic membrane which typically includes 70-80% of water. Hence, the illuminating reference wavelength of this range, e.g., 1440nm, while propagating towards the middle ear cavity is highly absorbed by the tympanic membrane and substantially does not reach the middle ear cavity therebehind; and thus the detected reflection is independent of whether water exists in the middle ear cavity or not. Even if a certain portion of incident light passes through the tympanic membrane (since the water absorption/transmission spectrum typically depends on the depth of water), this light portion is then highly absorbed by promontory which also includes water. These affects are irrespective of whether water exists in the middle ear cavity or not. The other possible reference wavelength range of 700-900nm is substantially transmitted by water. Hence, the illuminating reference wavelength, e.g., 830nm, is substantially transmitted by the tympanic membrane and through the middle ear cavity irrespective of whether it contains water or not, and is partially reflected by the promontory; the detected reflection is thus independent of whether water exists in the middle ear cavity or not.

The operating wavelength range (1200-1400nm; or 1500-1700nm) is partially absorbable by water. Hence, such wavelength (e.g., 1550nm) while propagating towards the middle ear cavity is partially absorbed by the tympanic

membrane, then partially absorbed by water, if any, in the middle ear cavity, and then reflected by the promontory. Hence, if water exists in the middle ear cavity (AOM or SOM condition), then the detected light intensity is decreased as compared to that of no water in the middle ear cavity (healthy condition). The detected reflection of the operating wavelength is thus indicative of the AOM or SOM condition.

Fig. 1B shows the water media transmission spectra (transmission as a function of wavelength), where graphs $\mathbf{R_1}$ and $\mathbf{R_2}$ correspond to the depth of water of, respectively, 0.3mm and 5mm. These functions are calculated theoretically from the water absorption coefficient spectra. Graph $\mathbf{R_1}$ demonstrates that with the incident light of reference wavelength (1420-1480nm) certain amount of incident light might pass thorough the tympanic membrane (which is of about 0.3m thickness). But, as indicated above, this light will be then highly absorbed by the promontory which also contains high amount of water (about 70-80 percent of water).

Fig. 1C shows the experimental results of applying the device of the present invention to numerous "healthy" and "AOM or SOM sick" patients. Two graphs $\mathbf{H_1}$ and $\mathbf{H_2}$ are shown, each presenting, in relative units, the intensity of detected light for 1550nm wavelength (operating wavelength) as a function of the intensity of detected light for 1440nm wavelength (reference wavelength); each point or group of point corresponding to measurement session (one or more measurements) as applied to a specific patient. Graphs $\mathbf{H_1}$ corresponds to the measurements on "healthy" patients, and graph $\mathbf{H_2}$ corresponds to the measurements on "sick" patients. As also shown in the figure, a certain range of the intensity values is considered when evaluating the measurement results. The experiments thus show that the technique of the present invention provides for clearly distinguishing between the healthy and sick conditions.

Using illumination with both the reference and operating wavelengths enables estimation of a "noise" part of the detected light, which is substantially the same for the reference and operating wavelengths and can thus be extracted from

measured data. This noise part is mainly associated with the light scattering at the outer surface of the tympanic membrane, which is typically a diffusing surface (since it has a small-feature surface relief), and is thus highly dependent on a distance (termed *"working distance"*) between the probe and the ROI. To this end, the probe is configured so as to ensure substantially the same optical path for both the reference and operating wavelengths, as will be described below.

Thus, in order to detect the AOM or SOM condition, the use of two illuminating wavelengths is sufficient. In the present example of **Fig. 1A**, these two wavelengths are generated by the same light source $\mathbf{LS_1}$, e.g., LED, and a common InGaAs detector $\mathbf{LD_1}$ is used for detecting the reflections of these wavelengths.

In order to detect the AOM condition (which differs from the SOM condition in the relatively high scattering from the fluid medium in the middle ear cavity due to impurities in water), the control unit may operate to identify a difference in the detected light intensity associated with an increased scattering. Alternatively or additionally, in order to identify the AOM condition, as well as to detect any other inflammation condition, the probe device is configured to detect a change in the hemoglobin level from that of the healthy condition. To this end, the operating wavelength $\lambda^{(h)}_{oper}$ of about 570-580nm (preferably 575nm) is selected, which is relatively highly absorbable by hemoglobin (absorption peak) and thus the detected reflection of this wavelength from ROI depends on the amount of hemoglobin in the ROI. As for the hemoglobin-associated reference wavelength $\lambda^{(h)}_{ref}$, the same wavelength range as that of the water-associated reference wavelengths may be used (e.g., 1440nm, 720nm or 830nm), where the light response of the ear to these wavelengths is substantially independent of changes in the ear condition, since these wavelengths are substantially non-absorbable by hemoglobin.

Fig. 1D shows the simulation results in the form of light absorption as a function of wavelength. Here, graphs $\mathbf{P_1}$ and $\mathbf{P_2}$ correspond to, respectively, to the healthy and sick conditions, and graphs $\mathbf{P_1}$ and $\mathbf{P_2}$ correspond to the standard

deviation for the same. The sick condition (increased concentration of hemoglobin) can thus be detected.

In the present example of **Fig. 1A**, the reference and operating wavelengths for hemoglobin level monitoring are generated by the same light source $\mathbf{LS_2}$, e.g., LED, and the reflections of these wavelengths are detected by a silicon detector $\mathbf{LD_2}$.

It should be noted that the provision of additional hemoglobin-associated reference wavelength (or wavelength range) is optional, and generally the use of three different wavelengths (or wavelength ranges) is sufficient for SOM and AOM measurements, namely one reference wavelength and two operating wavelengths. It should also be noted that as the otoscope typically defines an imaging channel for visual observation of the ROI by a physician, the same light source $\mathbf{LS_2}$ may be used in the imaging and hemoglobin measurement channels.

It should also be noted that, generally, the probe may be configured for spectral measurements using one or more light sources producing light including the desired wavelengths. A spectrometric detector arrangement (using a single or multiple light detectors) may be used for detecting the light response of ROI, in which case the detected spectrum is then analyzed to select therefrom light intensities corresponding to the desired wavelengths or wavelength ranges.

Turning now to **Figs. 1E and 1F**, there is schematically illustrated an example of arranging the fibers for directing illuminating light towards the ROI and for collecting reflected light and directing it towards the detection unit. As shown in **Fig. 1E** illustrating a cross sectional view of the distal end of the probe by which it is brought to the ROI, in this specific but non-limiting example, a fiber bundle **F** containing six fibers $\mathbf{F_1}$-$\mathbf{F_6}$ is used, four of them $\mathbf{F_1}$-$\mathbf{F_4}$ being illuminating fibers for transmitting four selected wavelengths $\lambda^{(w)}_{ref}$, $\lambda^{(w)}_{oper}$, $\lambda^{(h)}_{ref}$, $\lambda^{(h)}_{oper}$, respectively, from the light source(s) towards the ROI, and the other two fibers $\mathbf{F_5}$ and $\mathbf{F_6}$ being light collecting fibers for collecting the reflected light and transmitting it towards the detection unit. Again, it should be understood that a single illuminating fiber may be used for transmitting all the incident light wavelengths; and the provision

for the second reference wavelength is optional. As also shown in the figure in dashed lines, this fiber bundle **F** may be placed in the central region (of about 1mm diameter) of the probe's distal end (of about 4mm diameter), while a periphery region of the probe, outside the fiber bundle F, serves as an imaging (visual) channel **IC** for the propagation of reflected light to be used by a physician to visually observe the ROI and/or to be collected by an imaging device, as the case may be.

Generally, the fibers arrangement **F** is such as to ensure that all the incident light portions (from all the fibers) illuminate substantially the same spot in the ROI, and the illuminating and reflected light portions propagate substantially equal optical paths between the distal end of the probe and the ROI (working distance). To this end, the numerical aperture of each of the fibers $\mathbf{F_1}$-$\mathbf{F_6}$ is selected in accordance with the working distance **d** such that the output of the illuminating fibers $\mathbf{F_1}$-$\mathbf{F_4}$ presents a point-like light source for the illuminated spot, and the light collection is carried out with the same numerical aperture as the illumination.

Considering that the illuminated spot diameter **D** is to be of about 7-8cm, and that the working distance **d** is about 15mm, the illuminating fibers $\mathbf{F_1}$-$\mathbf{F_4}$, each having a 100μm core diameter, are located in a spaced apart relation so as to surround light collecting fibers $\mathbf{F_5}$ and $\mathbf{F_6}$ each having a 300μm core diameter. For example, the illuminating fibers are located at the corners of a rectangle (or arranged in a circular array). The light collecting fibers are located one adjacent to the other between the illuminating fibers. The numerical aperture of the fibers is such that an overlapping region between light spots produced by light portion from the fibers within the ROI is significantly larger than a space between these spots, practically the overlapping region is of about the desired spot size D, namely of about 7-8cm.

Turning back to **Fig. 1A**, it should be understood that the filtering unit **8** may include two spectral filters (e.g., dichroic beam splitters) accommodated at the output of the collecting fibers, respectively, and associated with respective light detectors.

It should also be noted that the probe may be formed with a speculum member at the distal end of the probe housing. The speculum member can be integral with the housing, or removably mountable onto the distal end of the housing, as will be exemplified further below. Referring to **Fig. 1E**, the peripheral region of the probe's distal end may be constituted by the speculum mounted onto the probe. The relative arrangement of the fiber bundle and the visual channel may be different from that exemplified in Fig. 1E. For example, the fibers may be located within the speculum, and the visual channel be represented by the central region of the probe.

An optical probe of the present invention may be configured for transmitting light emanating from a target tissue (constituting a region of interest) along at least two separate optical channels, and include a probe head and a speculum member removably fitted to a distal end of the probe head. The probe head includes light transmission means for directing illuminating light to the target tissue via a distal end of the speculum, and means for directing light emanating from the target tissue along at least two separate optical channels. The speculum member is adapted for positioning the distal end thereof proximate to the target tissue.

Unless otherwise stated, the term *"proximal"* (P) herein refers to a direction away from the target tissue and towards the user of the optical probe, while the term *"distal"* (D) refers to a direction towards the target tissue and away from the user.

Referring to **Fig. 2**, another example of an optical probe, generally designated **100**, is illustrated. The probe **100** includes a speculum member **10** removably fitted to a probe head **50**. The speculum member **10** is generally frustoconical in form, having a smaller distal end **11** with aperture **12**, and a larger proximal end **15**. The speculum member **10** is hollow, enabling optical communication between the aperture **12** and the proximal end **15**.

The probe head **50** is also typically frustoconical in form, the smaller distal end **51** thereof generally configured for engagement with the speculum member **10**. The inner conical surface of the proximal end **15** is typically configured to provide a press-fit engagement with the outer conical surface of the distal end **51** of the

probe head. Alternatively, suitable engagement means such as a bayonet fitting or complementary screw threads may be provided for removably fitting the speculum member **10** to the probe head **50**.

The probe head **50** is typically hollow, having a distal end **51** which is in optical communication with aperture **12** when the speculum member **10** is engaged with the probe head **50**. The probe head **50** has an objective **80** at the proximal end thereof, which may be an eyepiece ocular, for example, to permit direct visual observation of light passing through said aperture **12** along principal axis **99**. Alternatively, the objective **80** may comprise any suitable video camera or CCD device, for recording images transmitted from a target tissue **300** via the aperture **12**. The target tissue **300**, which may be the ear canal, or vaginal walls, for example, according to the specific application of the probe, is illuminated by light produced by one or more suitable light source **20** via an appropriately provided light transmission assembly such as a focusing element **22**. Alternatively, the light source is remote from the probe **100**, and suitable optical fiber(s) arrangement provides optical communication between the light source and the focusing element **22**. Advantageously, the light source **20** and/or the focusing element **22** are aligned with the outer wall of the probe head **50**, and thus at an angle with respect to the principal axis **99**. Accordingly, the speculum member **10** is provided with an internal reflector **18** configured to direct illuminating light incident thereon from said focusing element **22** towards the aperture **12** and therefrom to the target tissue **300** when this is in close proximity to the probe **100**.

As a result of illuminating the target tissue **300** with light, a light response (typically reflected light) of the tissue is produced which passes into the interior of the probe **100** via the aperture **12**. The probe head **50** comprises a beam splitter arrangement in the form of a parabolic mirror **60** having a central aperture **65**. By means of this aperture **65**, a first portion of light traveling from the distal aperture **12** along the principal axis **99** is directed towards a first optical channel and objective **80**, permitting visualization of the target tissue **300** either directly or indirectly. The parabolic mirror **60** has its axis of symmetry **92** inclined to the

principal axis **99** and directed towards a convex mirror **66**, positioned on the inner wall of the probe head, which in turn directs incident light thereon towards objective **68**. Thus, a second portion of light traveling from the distal aperture **12** parallel to the principal axis **99** is reflected by the parabolic mirror **60** and convex mirror **66** and thus directed towards a second optical channel and objective **68**. A suitable light sensor **69**, or alternatively a suitable optical fibre arrangement, is provided at objective **68**, and provides operative communication with a suitable analysis unit (preferably a spectrometer), to enable analysis of the light received from the tissue sample.

Referring to **Figs. 3 and 4**, yet another example of the optical probe, generally designated **200**, is illustrated. The probe **200** includes a speculum member **210** that releasably fits over the distal end **251** of the probe head **250**.

As with the example of Fig. 2, the speculum member **210** is generally frustoconical in form, having a smaller distal end **211** with aperture **212**, and a larger proximal end **215**. The speculum member **210** is hollow, enabling optical communication between the aperture **212** and the proximal end **215**.

The probe head **250** is also typically frustoconical in form, the smaller distal end **251** thereof generally configured for engagement with the speculum member **210**. The inner conical surface of the proximal end **215** is typically configured to provide a press-fit engagement with the outer conical surface of the distal end **251** of the probe head. Alternatively, suitable engagement means such as a bayonet fitting or complementary screw threads may be provided for removably fitting the speculum member **210** to the probe head **250**.

The probe head **250** is typically hollow, having a distal end **251** in optical communication and close proximity with aperture **212**. The probe head **250** has an objective **280** at the proximal end thereof, which may be an eyepiece ocular to permit direct visual observation of light passing through said aperture **212** along principal axis **299**. Alternatively, the objective **280** may comprise any suitable video camera or CCD device, for recording images transmitted from a target tissue **300** via distal aperture **212**. The target tissue **300**, which may be the ear canal, or vaginal

walls, for example, according to the specific application of the probe, is illuminated by means of a suitable light source **220** via a suitable light transmission means. In this embodiment the light transmission means comprises a waveguide arrangement in the form of a layer **240** of material having waveguiding properties, such as for example PMMA (polymethylmetacrylate) for example, and bonded or otherwise attached to the inner surface of the speculum member **210**. The waveguiding layer **240** has a transmission face **231** proximate to the aperture **212**, and a distal mating face **232** in optical communication with the transmission face **231**. Another waveguide **245** is provided in the probe head **250**, and having a mating face **246** at one end thereof complementary to said mating face **232**, and the other end of the waveguide **245** is connected to or connectable with the light source **220**. The light source **220** may optionally be remote from the probe **200**, and a suitable optic fibre arrangement provides optical communication between the light source and the wave guide **245**. Thus, when the speculum member **210** is properly engaged with respect to the probe head **250**, the mating faces **232** and **246** are aligned and in optical contact, enabling illumination light to be transmitted to the target tissue **300** via the transmission face **231**, when the probe **200** is in close proximity to the tissue **300**.

As with the example of Fig. 2, as a result of illuminating the target tissue **300** with light, a light response (typically reflected light) is produced from the tissue and passes into the interior of the probe **200** via the aperture **212**. The probe head **250** is typically hollow, enabling a first portion of light traveling from said aperture **212** along the principal axis **299** to be directed towards a first optical channel and towards objective **280**, permitting visualization of the target tissue **300** either directly or indirectly. In this embodiment, the second optical channel comprises a suitable second waveguide for directing light from said aperture **211** towards a light sensor. The second waveguide is in the form of a layer of material **270** having waveguiding properties comprised on the outer distal surface of the probe head **250**. The said second layer **270** is typically made from PMMA or the like, for example, and has a receiving face **271** proximate to the aperture **212**, and a transmitting face

272 in optical communication with the receiving face **271** and adapted for enabling light from outside of aperture **212** to pass therethrough to said second transmitting face **272**. The transmitting face **272** is adapted for optical communication with a suitable light sensor, directly or indirectly, or alternatively with a suitable optical fibre arrangement, which provides operative communication with a suitable analysis unit, typically a spectroscope, enabling analysis of the light received from the tissue sample. Preferably, the layer **270** is circumferentially covered by a protective layer **277**, made of for example metal or plastic, for minimizing damage to the waveguide, particularly during engagement and disengagement of the speculum member **210**.

Preferably, the probe **200**, and at least the probe head **250**, is accommodated in a suitable housing **295**, which also comprises a handle **296** to facilitate handling of the probe by the user.

In all embodiments, the speculum member is preferably disposable after one or multiple use with one patient, and is thus preferably made from a relatively inexpensive material.

Preferably, but optionally, the speculum member includes a plug (which is not specifically shown) that closes the distal aperture thereof. The plug is mounted so as to be shiftable from its operative position when it closes the aperture and thus is in the optical path of light propagating through the probe when in operation, and an inoperative position when it is out of said optical path. The plug at least at its inner surface is made from a suitable material that diffuses and reflects incident light thereon, and thus may be used by the optical probe of the present invention for calibration purposes. Thus, prior to using the optical probe with a patient, the intensity of diffused reflected light obtained via the second channel when the plug is internally illuminated by the illuminating light may be compared to the intensity of the illumination light. The ratio of intensities thus obtained is the compared with expected nominal datum values, and any deviation therefrom may then be applied to any qualitative measurements of intensities taken of the target tissues, the plug having being removed before such measurements.

In another aspect, the present invention relates to a measurement system and method for use in determining the patient's condition, in particular the ear condition. More specifically the system is used for determining whether the ear is healthy or is infected with otitis media or serous otitis media, and is therefore described below with respect to this specific application.

Referring to **Fig. 5**, an optical measurement system, generally at **400** is schematically illustrated. The system **400** is configured for determining the condition of a patient's ear. The system **400** comprises such main constructional parts as an optical measuring unit **402** for applying spectral measurements to the inside of the patient's ear; and a control unit **404** connectable to the measuring unit either via a communication cable or wireless communication means.

The measuring unit **402** is an optical probe, which may be designed as either one of the above-described examples. Generally, the measuring unit **402** includes a light source assembly (illumination unit) **406** for producing illuminating radiation of one or more predetermined wavelength range, for example 400-1600nm; a detector assembly (detection unit) **408** for receiving light response of the illuminated region in the ear (light reflected from the illuminated region) and generating measured data indicative thereof. The optical probe also preferably includes appropriate light transmitting arrangement defining measurement channels(s) and also defining an imaging (visual) channel IC shown in the figure in dashed lines. As indicated above, light produced by the same one or more of light source elements of the illumination unit **406** may be used for the measurement and imaging channels. The detection unit **408** may be configured as a spectrometer or may include at least two detectors for detecting light of different wavelength ranges. The measuring unit preferably also includes a light directing assembly for spatially separating incident and reflected light. These may for example be optical fibers, and/or mirrors' arrangement.

The control unit **404** is typically a computer system including *inter alia* a memory utility **410** for storing certain reference data; a data processing and analyzing utility **412**; and a user interface utility **414**. The data processing and

analyzing utility is preprogrammed for processing input measured data by applying thereto a predetermined mathematical model.

The reference data is obtained by performing a general learning mode, and carrying out a calibration stage prior to applying a measurement session to a specific patient. The learning mode consists of applying numerous measurements to various patients and determining measured data corresponding to healthy conditions.

According to one embodiment of the invention, the reference data includes light intensities corresponding to the light response of the healthy ear at several selected wavelengths or wavelength ranges of incident light, e.g., at least one reference wavelength and at least one operating wavelength considering that SOM condition is to be detected or at least two operating wavelengths considering that AOM is to be detected.

According to another embodiment of the invention, the reference data includes, per each disease to be detected, a value or a range of values for at least one spectral factor defining a boundary between the healthy and diseased condition. The spectral factor is determined by processing measured spectral data in the form of a relative spectrum of the ROI (relative light intensity as a function of wavelength) with the predetermined mathematical model, as will be described below.

The method of the present invention will now be exemplified with reference to **Figs. 6A and 6B** and **Figs. 7A-7B, 8A-8B**.

Figs. 6A and 6B show two examples, respectively, of a flow diagram of the invented method. In both examples, initially, a calibration stage is preferably carried out - Step I. Generally, the calibration stage is aimed at eliminating or at least significantly reducing the effects of variation in the light source and detector response in the measured data. Such variations exist between different instruments, and different times, even on the same instrument. At the calibration stage, a white reference spectrum, $R_W(\lambda)$, is obtained. This can be implemented as described above, namely, by placing a highly reflective (preferably, diffusive reflective)

element at the distal end of the measuring unit (in the case of otoscope, the distal end of a speculum) and operating the measuring unit to determine the reflectivity of this white surface, which is considered to be equal to the intensity of incident light reaching the region of interest.

Then, an actual measurement session (at least one measurement of a predetermine duration) is applied to the region of interest (e.g., patient's ear) – Step II. The region of interest is illuminated with predetermined incident radiation, reflected light is detected, and measured data is produced. According to the example of **Fig. 6A**, the actual measurement session includes illuminating the ROI with at least two different wavelengths or wavelength ranges (preferably, at least three different wavelengths) as described above with reference to Figs. 1A-1D. The illumination is preferably carried out in pulses, e.g., 1msec pulse, and the measurement session (illumination/detection) duration is of about 100msec. Measured data is indicative of the reflections of the ROI to the illuminating wavelengths, λ_{ref} (or two different reference wavelengths), $\lambda^{(w)}_{oper}$ and $\lambda^{(h)}_{oper}$. This measured data may be derived from spectral data. According to the example of **Fig. 6B**, the ROI is illuminated with broadband illumination and the measured data is in the form of spectral data (the detected light intensity as a function of all the wavelengths of the incident light).

Figs. 7A and 7B exemplify, respectively, the ear spectrum (measured spectral data) and white spectrum (reference spectral data). In the specific, but non-limiting, example of determining the patient's ear condition, incident light of 300-1400nm is used. The white spectrum is obtained prior to applying the actual measurement session to each patient (at the calibration stage) and is stored in the memory utility. It should be noted that, generally, the calibration stage may be conducted periodically and not necessarily repeated for each new patient.

The measured data is received at the control unit where it is processed and analyzed with the predetermined mathematical model – step III.

According to the example of **Fig. 6A**, the processing of the measured data consists of determining, for water and hemoglobin, a relation between the detected

light intensity (reflection) for the operating wavelength and the detected light intensity for the reference wavelength, namely, the light intensity for operating wavelength, $I^{(w)}_{\lambda oper}$, as a function f_1 of the light intensity for the reference wavelength, $I_{\lambda ref}$, and similarly for hemoglobin, $I^{(h)}_{\lambda oper}=f_2(I_{\lambda ref})$, where the reference wavelength may be the same of different for water- and hemoglobin-related measurements. The measured intensity may be calculated as integral of the detected light pulses during the measurement session (as in the example of Fig. 1C). The output data in then generated being indicative of whether the patient's ear is classified to "healthy", "AOM" or "SOM" condition. If the reflection of water-associated operating wavelength falls within the predetermined range of "normal" intensities (see Fig. 1C) then the patient's condition is considered as "healthy" (where "normal intensity range is defined as reference data or calibration curve); if the reflection of water-associated operating wavelength is lower than the "normal" intensity (considering a certain threshold) and the reflection of hemoglobin-associated wavelength corresponds to "normal" hemoglobin level, then the patient's condition is considered as relating to SOM; and if the reflection of water-associated operating wavelength is lower than the "normal" intensity and the reflection of hemoglobin-associated wavelength is lower than the "normal" one, then the patient's condition is considered as relating to AOM.

According to another embodiment of the invention, the processing of the measured data consists of normalizing the measured spectrum by the reference spectrum to obtain a normalized reflectivity spectrum $R(\lambda)$. The normalized reflectivity spectrum is then processed to determine a corresponding value of at least one measurable parameter (the so-called "spectral factor"). The normalized reflectivity spectrum $R(\lambda)$ is independent of instrument number j and of time t.

Mathematically, the normalization process can be described as follows:

$$E_j(\lambda,t) = A\, I_j(\lambda,t)\, R_E(\lambda)\, D_j(\lambda,t)$$

$$W_j(\lambda,t) = B\, I_j(\lambda,t)\, R_W(\lambda)\, D_j(\lambda,t)$$

wherein:

$E_j(\lambda,t)$ is the measured spectrum of the region of interest (e.g., ear);

$W_j(\lambda,t)$ is the measured white reference spectrum;

j is the instrument number;

t is the time;

λ is the wavelength of incident light;

A,B are unknown amplitudes;

$I_j(\lambda,t)$ is the illumination spectrum of light source for instrument j;

$D_j(\lambda,t)$ is the response spectrum of the detector for instrument j;

$R_E(\lambda)$ is the reflectivity spectrum of the ear drum;

$R_W(\lambda)$ is the reflectivity of a standard white surface

The normalized reflectivity spectrum is determined as:

$$R(\lambda) = E_j(\lambda,t) / W_j(\lambda,t) = C\, R_E(\lambda) / R_W(\lambda)$$

Here, parameter *C* is an unknown amplitude, which depends *inter alia* upon the signal integration time and the distance of the instrument from the patient's ear drum. To eliminate the effect of parameter *C*, the normalized reflectivity spectrum is further normalized by a certain wavelength λ_0 from the incident light spectrum. In the present example, this is implemented by setting a relative spectrum: $r(\lambda) = R(\lambda) / R(\lambda_0)$, so that $r(\lambda_0) = 1$, wherein λ_0 is chosen in the center of the wavelength range of incident light (e.g., visible spectrum), and $r(\lambda)$ is a "relative" spectrum, insofar as all intensities are measured relative to the intensity at λ_0.

An example of the relative spectrum of a sample is shown in **Fig. 8A**. In this specific example of determining the patient's ear condition for the purposes of detecting the existence of serous otitis media (SOM) and acute otitis media (AOM), the normalized spectrum for 400-1000nm is determined. The value of λ_0 is chosen in the center of this range, namely to be about 700nm.

The inventors have found that a specific disease is characterized by at least one predetermined spectral range, from the entire measured spectrum, where the spectral behavior of the light response is maximally affected by the disease. For example, in order to detect the existence of serous otitis media (SOM) and acute

otitis media (AOM), the spectral ranges of interest may be 500-650nm (visible range) and 800-1550nm (IR range) respectively.

The processing of the relative spectrum $r(\lambda)$ generally consists of applying the predetermined model to either the entire normalized spectrum or at least one selected region of this spectrum (region characterized by the maximal effects of a specific disease). In this specific example, the mathematical model utilizes a Likelihood Algorithm, and the processing consists of the following:

The relative spectrum $r(\lambda)$ is sampled at certain discrete wavelengths, to generate a feature vector, $\underline{r}$:

$$\underline{r} = \{ r(\lambda_n), n = 1, 2 \ldots N \}$$

Two populations are considered: (A) healthy ears and (B) infected ears. By doing clinical tests on a large sample of ears of both types, the probability densities $f(\underline{r} \mid A)$ and $f(\underline{r} \mid B)$ are learned. For example, using Gaussian probability densities,

$$f(\underline{r} \mid A) = g(\underline{r}, \underline{\mu}_A, P_A)$$

$$f(\underline{r} \mid B) = g(\underline{r}, \underline{\mu}_B, P_B)$$

wherein

$$g(\underline{r}, \underline{\mu}, P) = [2\pi \det(P)]^{-N/2} \exp [-1/2 (\underline{r} - \underline{\mu})^T P^{-1} (\underline{r} - \underline{\mu})]$$

$$\underline{\mu} = \text{mean}(\underline{r})$$

$P = \text{covariance}(\underline{r}) = \text{NxN matrix}$

A new patient arrives, and his ear spectrum is measured. His feature vector is denoted by $\underline{x}$. In order to diagnose the ear as healthy or infected, the algorithm forms the log-likelihood ratio:

$$L1(\underline{x}) = 2 \log \{ f(\underline{x} \mid B) / f(\underline{x} \mid A) \}$$

$$= (\underline{x} - \underline{\mu}_A)^T P_A^{-1} (\underline{x} - \underline{\mu}_A) - (\underline{x} - \underline{\mu}_B)^T P_B^{-1} (\underline{x} - \underline{\mu}_B)$$

Then:

If $L1(\underline{x}) \leq T1$, diagnosis = A (healthy)

If $L1(\underline{x}) > T1$, diagnosis = B (infected)

The numerical value of the threshold T1 is chosen to achieve a desired level of sensitivity (i.e., the probability of correctly diagnosing an infected ear).

Considering next the subdivision of infected ears into 2 classes: (B_1) serous otitis media (SOM) and (B_2) acute otitis media (AOM), if $\underline{x}$ is diagnosed as infected ($L1(\underline{x}) > T1$), a second log-likelihood ratio is formed:

$$L2(\underline{x}) = 2 \log \{ f(\underline{x} \mid B_2) / f(\underline{x} \mid B_1) \}$$

$$= (\underline{x} - \underline{\mu}_{B1})^T P_{B1}^{-1} (\underline{x} - \underline{\mu}_{B1}) - (\underline{x} - \underline{\mu}_{B2})^T P_{B2}^{-1} (\underline{x} - \underline{\mu}_{B2})$$

and diagnosis is made as follows:

If $L2(\underline{x}) \leq T2$, diagnosis = B_1 (SOM)

If $L2(\underline{x}) > T2$, diagnosis = B_2 (AOM)

wherein, again, T2 is a threshold which is chosen to achieve a desired level of sensitivity (i.e., the probability of correctly diagnosing AOM).

Fig. 8B shows the values of the measurable parameters L1 and L2 for normal (NOR), SOM and AOM conditions in the two-dimensional likelihood space, as obtained for the specific example of Figs. 6A-6C.

The values L1 and L2 (log-likelihood) actually present the spectral factors being in the well-defined association with the value or range of values corresponding to the healthy condition of the ear and can thus be used by the physician for decision making. Preferably, these values L1 and L2 are further scaled to produce "spectral factors" that may be of better diagnostic value to a physician. They are continuous numbers that, over time and experience, may have value for borderline cases, much in the way that blood counts and iron levels in the blood are measured in continuous fashion. The following is the example of such scaling:

$$S1(x) = a1 + b1 * (L1(x) - T1)$$

$$S2(x) = a2 + b2 * (L2(x) - T2)$$

Here, coefficients a1, a2, b1 and b2 (that need not be necessarily different from each other) are appropriately selected to provide a scale which can be easily remembered by the physician, and thus facilitating the decision making.

The technique of the present invention thus provides for automatically determining the patient's condition by obtaining and analyzing the light response of the region of interest to predetermined wavelengths or wavelength ranges, and provides for effective collection of the light response. Output data presented to a

physician (displayed on the monitor of the control unit) may include just the calculated spectral factor and preferably also the value or range of values for the spectral factor at normal (non-diseased) condition; or may include even clear "yes" and "no" results.

Those skilled in the art will readily appreciate that various modifications and changes can be applied to the embodiments of the invention as hereinbefore described without departing from its scope defined in and by the appended claims.